Kidney International, Vol. 4 (1973), p. 146–153

The influence of a high calcium carbonate intake on bone disease in patients undergoing hemodialysis

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Bone disease is one of the most common features of protracted uremia. It is due to a host of metabolic derangements, including an acquired defect in vitamin D metabolism, hypersecretion of parathyroid hormone, abnormalities in the renal handling of phosphate and chronic acidosis. The influence of maintenance hemodialysis on uremic osteodystrophy is still a matter of controversy regarding the rate of progression and the severity of skeletal disease, and the distribution of calcium and phosphate in the body following long-term treatment. This is especially true of the therapeutic policy of increasing the serum calcium concentration and thus inhibiting the secretion of parathyroid hormone.

This study was undertaken to compare bone disease in two groups of patients, one treated with a dialysate calcium fixed at 6 mg/100 ml (which corresponds to the normal value for ultrafilterable calcium), and a second group that was treated additionally with a large daily intake of calcium carbonate in an attempt to increase the intestinal absorption of this ion. The results indicate that a) the latter regimen was capable of significantly reducing the rate of bone resorption and recalcifying osteomalacic lesions, and b) since serum calcium concentrations did not significantly differ in the two groups, the patients treated by dialysis alone presumably maintained their serum calcium concentration at the expense of their skeleton calcium stores.

Materials and methods

Patients. The 55 study patients were selected from 124 patients treated in our chronic hemodialysis center from January 1968 to December 1972. Their selection was based on the following criteria: 1) consistent data on the cause of their nephropathies, the duration of azotemia before dialysis, and radiological and biochemical status when dialysis was initiated; 2) regular follow-up for at least 8 months after initiation of hemodialysis; and 3) adequate information on the duration of dialysis sessions, the composition of the dialysate and the drugs taken during the follow-up period.

Dialysis procedure. All patients were treated by biweekly hemodialysis, with Travenol UF-145 coils. Patients of group I were treated in our in-center hemodialysis unit, using a central delivery system. Ten patients of group II were studied in the hospital during training for home dialysis and after they had started treatment in the home. For all, dialysate was prepared by mixing softened water with concentrate, 29:1, v:v. The final composition of dialysate was (mEq/liter): Na = 138; K = 1.5; Cl = 106; acetate = 38; Ca = 3; Mg = 1.5. The fluoride content of the water was not measured but it was presumably the same for all during the study. The dialysate flow rate was 0.8 to 1 liter/min with a single pass, recirculation system. Cimino-Brescia fistulas were used; the blood flow-rate was 100 to 250 ml/min; the duration of dialysis was 7 to 9 hr, according to the patient's body weight.

Diet and drugs. All patients were allowed a free protein intake and advised to take Kayexalate®, 5 g daily. No data were available concerning their dietary intake of calcium, but it was consistently low, as was their sun exposure. Supplements of vitamin D were not prescribed.

The patients were separated into two groups according to the prescription of calcium carbonate and aluminium hydroxide gel. Group I was composed of 24 patients treated by dialysis alone without calcium supplements. In some, aluminium hydroxide gel was prescribed to treat metastatic calcifications associated with high Ca × P products. Group II was composed of 31 patients treated from the very beginning by dialysis and calcium carbonate, 5 to 20 g/day. Their calcium intake was thus increased 100 to 400 mEq/day above that in group I. In addition, they were prescribed aluminium hydroxide gel, 2 to 5 g/day.

One can be almost certain that the supplements of tasteless calcium carbonate were taken by the majority of patients. This is not true of aluminium hydroxide gel, which was often taken irregularly because of poor gastrointestinal tolerance.

Serum chemistries. In all patients, blood samples were taken twice a month before dialysis for the analysis of calcium (complexometry), phosphorus (ammonium molybdate) and alkaline phosphatase (sodium phenyl phosphate hydrolysis), and after dialysis for calcium and phosphorus measurements.

Roentgenographic follow-up. Every four months, radiographs of the skeleton and of the joints were obtained. X-rays were evaluated by the same physician throughout the study. Soft tissue calcifications were quantified from 0 to 4+.

Bone histology. In all patients of group I and some of group II, serial bone biopsies were performed every four to six months, with two to six consecutive biopsies per patient. The methods and results of this study have been described elsewhere [1].

Results

Comparison of the two groups of patients before maintenance hemodialysis

Table 1 analyzes the characteristics of the two groups before the initiation of dialysis. The ages and sex ratios were not significantly different. The duration of azotemia before the study began was slightly shorter in group II due to a greater number of patients with chronic glomerulonephritis in group I versus slowly progressive chronic pyelonephritis in group II. Both groups were comparable in terms of predialysis biochemical measurements: statistical analysis did not exhibit significant differences between serum calcium (group I: 8.38 ± 0.38 mg/100 ml; group II: 7.80 ± 1.05 mg/100 ml); serum phosphorus (group I: 8.68 ± 0.77 mg/100 ml; group II: 8.43 ± 1.22 mg/100 ml) or serum alkaline phosphatase (K.A. units: group I, 12.94 ± 3.16; group II, 10.52 ± 2.56). The scope of bone lesions observed in systematic biopsies in group I has been analyzed elsewhere [1, 2]. Only a few bone biopsies were performed in group II before dialysis was begun. We cannot then compare the two groups in terms of quantified histological bone lesions, but as far as radiological data can be relied upon, severe resorption, severe osteomalacia and mild bone lesions were similarly distributed. Radiological evidence of marked bone disease was present in 13 patients in group I (54.2%) and 15 in group II (48.3%).

Table 1. Main characteristics of the study groups before starting maintenance hemodialysis

	Group I	Group II
No. of patients	24	31
Mean age, *yrs*	$33^1/_2$	$34^1/_2$
Diagnosis:		
chronic glomerulonephritis	9	14
chronic pyelonephritis	9	10
congenital	3	3
vascular	1	1
unknown	—	2
miscellaneous	2	1
Duration of azotemia, *yrs*	5.5	4.9
Radiological and/or histological evidence of bone disease	13	15

Group I: Dialysis alone.
Group II: Dialysis + high intake of calcium carbonate.

Comparative evolution during the course of hemodialysis

The same patients were kept under observation and followed for two years, and the number of cases progressively decreased as patients were transplanted or died. We have compared the biochemical, radiological and clinical data at 4, 8, 12, 18 and 24 months after their first hemodialysis.

Serum chemistries

Calcium. There was a significant difference between the serum levels of calcium in the two groups at four months ($P < 0.02$), due to a considerable rise of serum calcium in some patients of group II. Such hypercalcemia occurred within six weeks after the concomitant initiation of dialysis

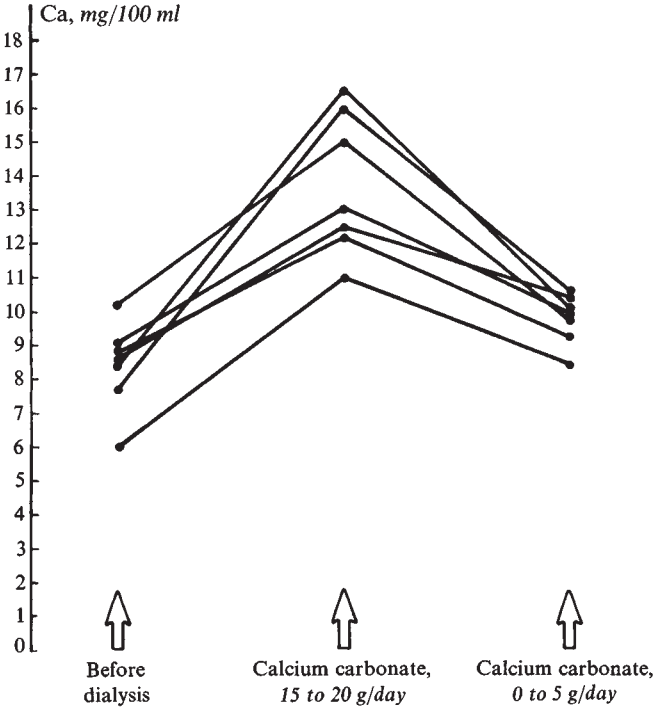

Fig. 1. *Hypercalcemia due to calcium carbonate overdosage.*

and calcium therapy. In others the hypercalcemia was somewhat delayed, especially in patients placed on home dialysis. In three of the latter, hypercalcemia was associated with marked hypophosphatemia (serum P less than 3 mg/100 ml, before dialysis), probably due to excessive dietary restriction of phosphate and excess intake of aluminium hydroxide gel. Fig. 1 records the seven cases of hypercalcemia due to calcium carbonate overdosage. The signs and symptoms of calcium intoxication appeared gradually. The main clinical features were loss of appetite and mental dullness. After tapering the dosage of calcium carbonate, hypercalcemia subsided rapidly. It is worth noting that those patients did not exhibit more radiological signs of hyperparathyroidism than the others. At eight months and thereafter, there was no significant difference in serum calcium levels between the two groups (Fig. 2).

Phosphorus. A marked fall in serum phosphorus was seen in group II at four months, with a very significant difference from the results observed in group I ($P<0.001$). This was no longer the case from the eighth month (Fig. 3).

Alkaline phosphatase. There was no difference between the two groups four months after the beginning of dialyses. At eight months, the mean level of the enzyme started to rise in group I and continued to increase steadily thereafter to reach very high levels at one year (Fig. 4).

A statistical analysis of the relationship between the alkaline phosphatase levels and the quantitative histological lesions on the bone biopsies disclosed a very significant relationship between the surface of osteoclastic resorption and the alkaline phosphatase level ($N=91$; $r=0.34$, $P<0.001$). In group II, alkaline phosphatase levels remained remarkably stable throughout. Thus, from the first year and thereafter, there evolved a clear-cut difference between the two groups as regards the rate of bone resorption.

Bone lesions

The evolution of bone disease in group I was followed by roentgenographic investigation and serial bone biopsies. When bone resorption was predominant before hemodialysis, it progressively diminished, although the amount of osteoid tissue increased in some of these patients. When osteomalacia was the major initial feature, recalcification of the osteoid seams occurred within one year of dialysis; from then on, increasing resorption was seen parallel with rising alkaline phosphatase levels. When bone lesions were initially moderate, they remained so, except in one case where increasing resorption progressed until renal transplantation was done. There was good correlation between osteoclastic resorption and radiological evidence of hyperparathyroidism [1, 2].

In group II, the bone lesions were estimated from X-rays except in a few patients who had bone biopsies. The number

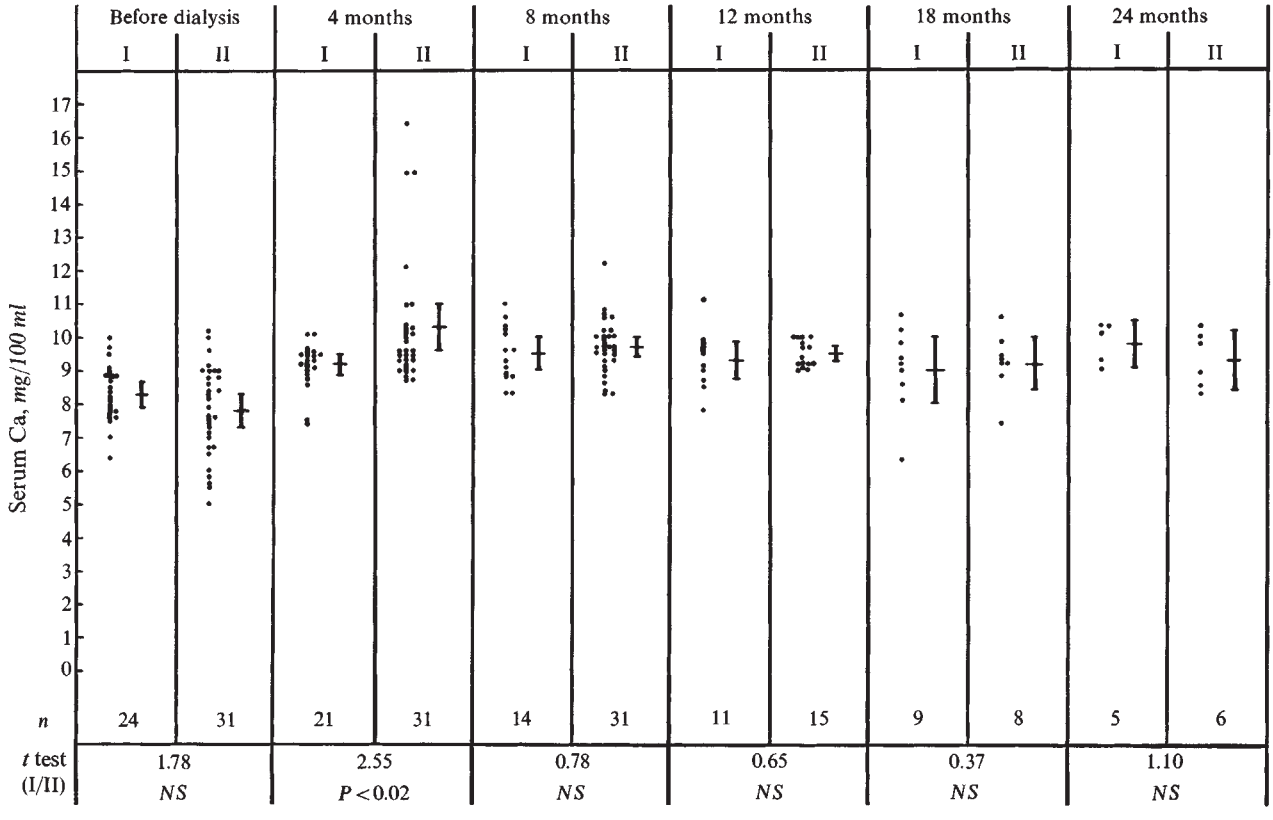

Fig. 2. *Comparative evolution of serum calcium.*

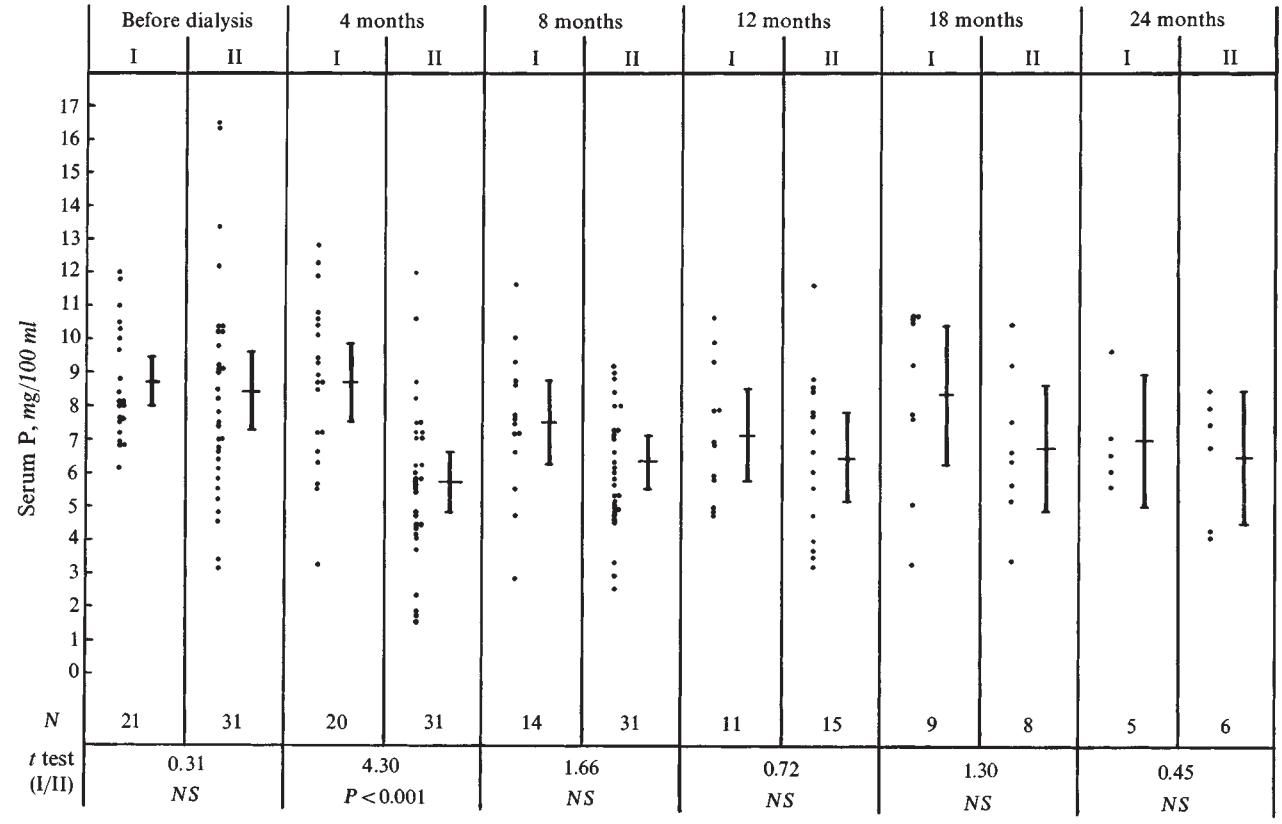

Fig. 3. *Comparative evolution of serum phosphate.*

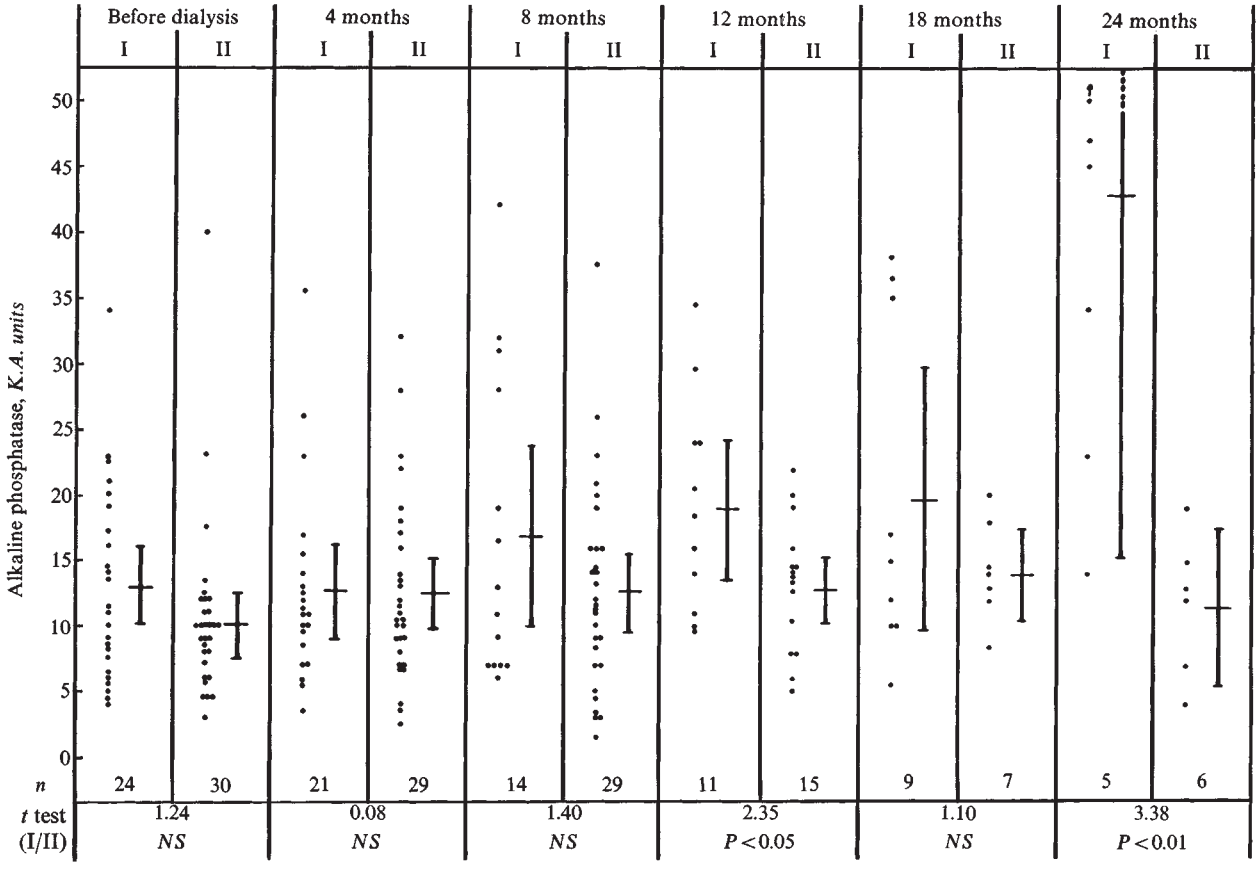

Fig. 4. *Comparative evolution of serum alkaline phosphatase.*

of cases with severe resorption was significantly different at 8 months: seven of 14 in group I and three of 31 in group II. Two years after initiation of dialysis, this difference was even more apparent, though the reduced number of patients followed makes comparisons somewhat difficult. Four of the five remaining patients in group I had evidence of severe resorption, and two had to be treated by three–fourths parathyroidectomy, whereas out of the six remaining cases of severe resorption in group II, one exhibited moderate resorption and the others had minimal changes of their bone structure and transparency.

Table 2. Main complications in the course of maintenance hemodialysis

Complications	Group I	Group II
Pseudogout attacks and/or metastatic calcifications	9/24	2/31
Spontaneous fractures (ribs)	3/24	0/31
Parathyroidectomy for hypercalcemia and severe resorption	2/14	0
Roentgenographic evidence of severe bone lesions 8 months after the beginning of hemodialysis	7/14	3/31

Clinical course

Table 2 summarizes the clinical complications noted in the two groups. Attacks of pseudogout and/or metastatic calcifications occurred in nine patients of group I but only two of group II. They afflicted patients with Ca × P products far above 70 and only those who exhibited radiographic and histologic signs of secondary hyperparathyroidism. In two patients, subtotal parathyroidectomy was performed because of extensive resorption and hypercalcemia. Spontaneous fractures of one or several ribs occurred in four patients of group I, three of whom had severe osteoclastic resorption. In the fourth, bone biopsy disclosed severe osteomalacia, 18 months after the first dialysis (Fig. 5a). At that time, treatment with calcium carbonate, 20 g/day was started; four months later, a second bone biopsy disclosed the onset of recalcification of osteoid tissue (Fig. 5b). After eight months of therapy, a third biopsy showed that the bone trabeculae were recalcified, with only thin layers of osteoid buried within mineralized

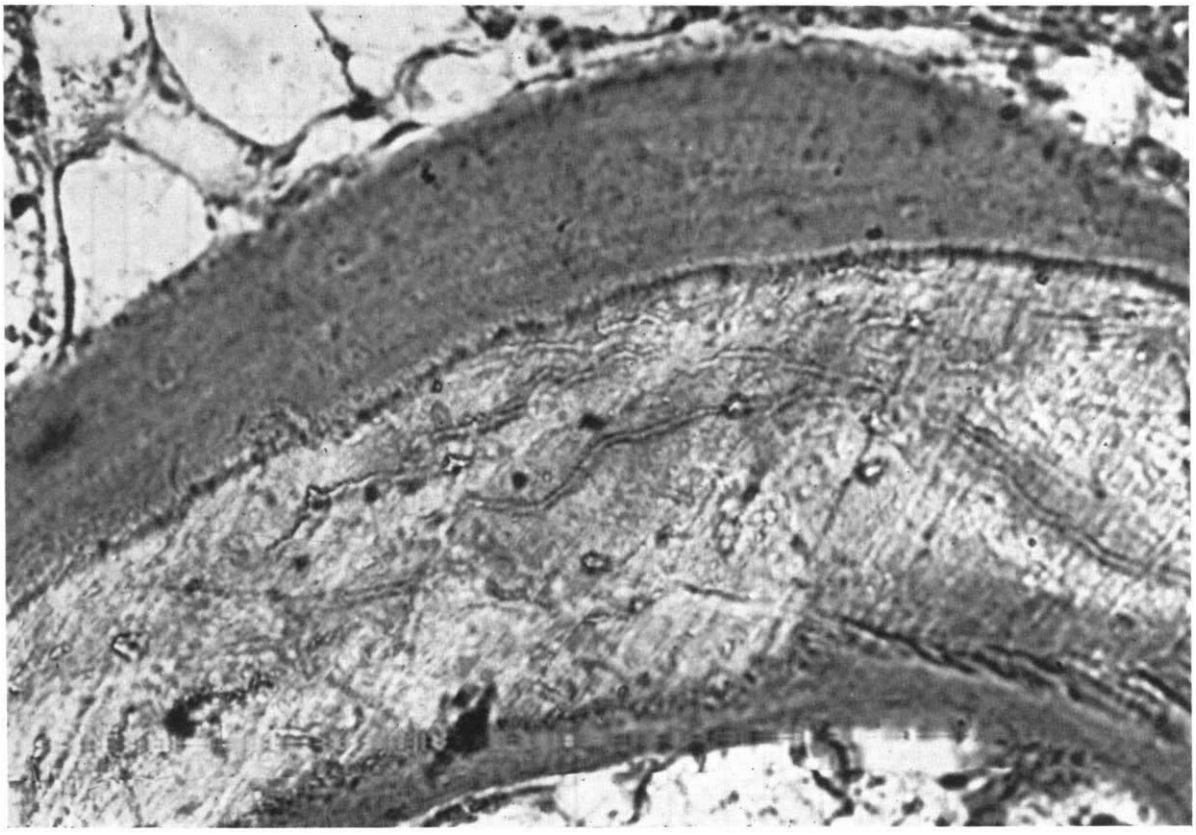

Fig. 5a

Fig. 5. a) *Undecalcified bone biopsy: severe osteomalacia;* b) *Same patient; biopsy taken after 4 months of high calcium carbonate intake (20 g/day); remineralization starts within the osteoid seams.* c) *After 8 months of calcium carbonate therapy, remineralization is almost complete, with remains of buried osteoid.* Fuchsin red stain, × 250.

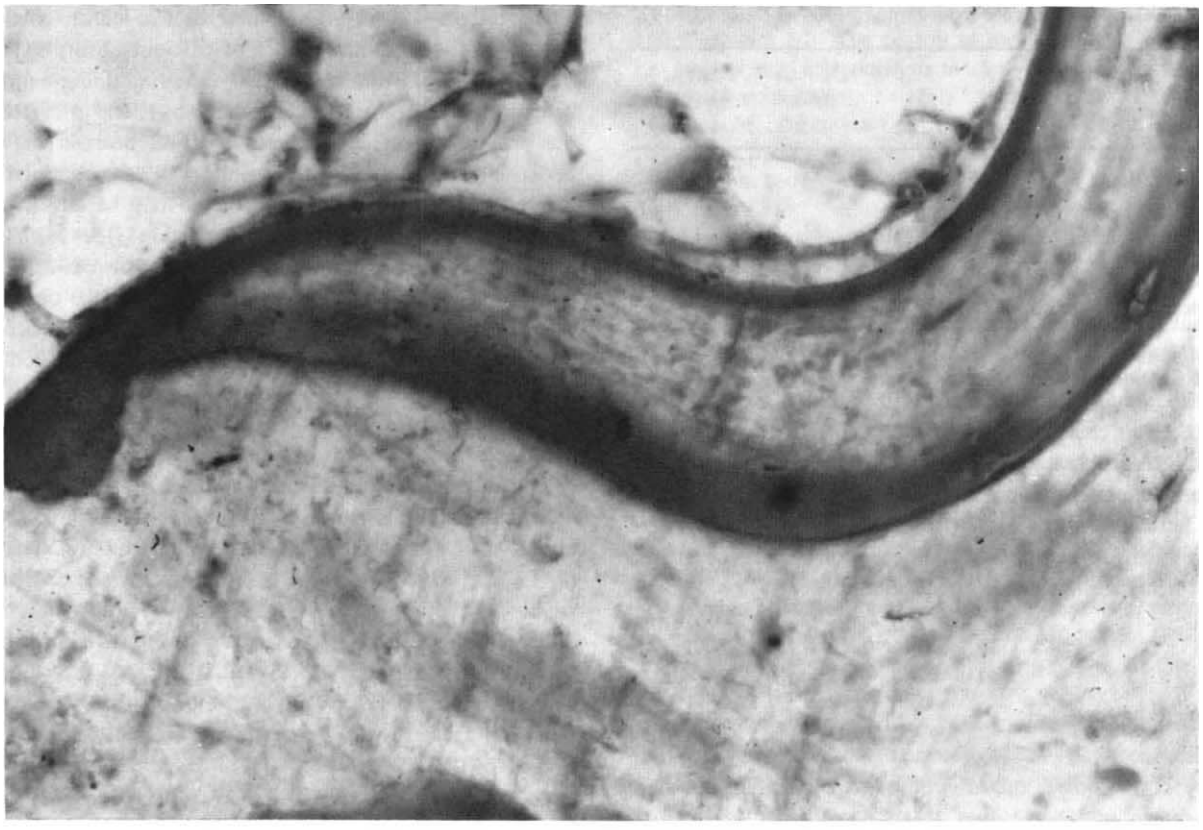

Fig. 5b

Fig. 5c

Table 3. Overall experience from January 1968 to December 1972

Treatment	Dialysis alone	Dialysis+ high calcium intake
No. of patients	33	91
Pseudogout attacks and/or metastatic calcifications	17	3
Spontaneous fractures	4	0
Necessity for parathyroidectomy	5	0
Evidence of severe bone disease	17	5

areas (Fig. 5c). Table 3 sums up the overall experience of our dialysis center from January, 1968, to December, 1972, and includes cases rejected from this study because of incomplete information. It indicates that about one-half of the patients treated with dialysis alone developed severe osteodystrophy, compared to one out of 18 in those treated with a high calcium carbonate intake.

Discussion

Chronic renal failure leads to progressive alterations of bone collectively that are termed "renal osteodystrophy." They consist of a mixture of osteomalacia, osteoclastic resorption and sometimes osteosclerosis, and they progressively increase with the duration of azotemia. Renal osteodystrophy is often associated with a redistribution of the calcium and phosphate ions in the body, mainly in the form of extra-skeletal calcifications.

The pathophysiology of these disorders is complex [3]. The bone is a victim of intricate metabolic disturbances [3–5]. Among these, the acquired impairment of intestinal calcium absorption, due to a lack of transformation of vitamin D into biologically active polar metabolites, undoubtly plays a major role [6]. A negative calcium balance and persistent hypocalcemia lead to defective mineralization and a permanent stimulation of parathyroid secretion [7]. Phosphate retention promotes both further hypocalcemia and soft tissue deposition of calcium phosphate [8, 9].

Maintenance hemodialysis abruptly modifies some of these disturbances such as chronic acidosis. On the other hand, it has less influence on the serum phosphorus concentration, the source of which is both exogenous (from the diet) and endogenous (from the resorbing bone). Also, it does not modify the defect of calcium absorption in the intestine [10]. The appropriate concentration of calcium in the dialysate is still not a matter of agreement in all dialysis centers. Wing [11] showed that movement of calcium from the bath occurs in hypocalcemic patients during dialysis when the concentration of this ion equals the normal level of ultrafilterable calcium, i.e., 6 mg/100 ml. It has been shown that the net transfer of calcium increases from 0 to 2 mg/min as the concentration varies from 5 to 10 mg/100 ml [12, 13]. Thus, dialysis can be an efficient bypass to the intestinal defect of calcium absorption. In fact, treating patients with a dialysate containing 6 mg of calcium per 100 ml appears to be insufficient in arresting the progression of hyperparathyroidism, both in the experience of others [8, 14] and in our own patients. Increasing the concentration to 8 mg/100 ml may be effective in reducing parathyroid hormone secretion [15, 16]. This increment of calcium concentration is not devoid of risks. Some patients may develop symptoms when the dialysate calcium reaches 7 mg/100 ml [11]. Also, the incidence of soft tissue deposits may increase [9, 17] if adequate control of the $Ca \times P$ product is not achieved by supplements of aluminium hydroxide gel. Others have not observed an increased incidence of clinically significant soft tissue calcification, although calcium content of skin increased significantly [18]. Uncertainty also exists concerning advisability of treatment with pharmacologic doses of vitamin D [9, 19, 20], which can lead to widespread tissue calcinosis when predialysis serum phosphorus is not maintained under 6 mg/100 ml. An alternative method of improving the calcium balance is the ingestion of large amounts of calcium salts. Clarkson [21, 22] showed that in chronic renal failure there was a daily increase in calcium absorption of 26 to 34.5 mg when 20 g of calcium carbonate was added to the diet. Curtis [14] demonstrated that calcium carbonate is effective in raising the serum calcium and lowering both bone resorption and the alkaline phosphatase activity in patients treated with hemodialysis. In the long-term observations, nevertheless, hypercalcemia occurred and there was a necessity for surgical parathyroidectomy.

Our experience is more in favor of a sustained benefit from a high daily calcium intake in the course of dialysis, without the drawbacks of increasing the calcium concentration in the bath. The efficiency of this regimen is supported both by clinical arguments and by the study of bone biopsy specimens. Hypercalcemia was seen in seven patients out of 31 of group II soon after the simultaneous institution of dialyses and calcium therapy, and it was never observed in patients treated by dialysis alone, even in the face of concomitant hypophosphatemia. This shows that, even in advanced renal failure, and whatever the initial serum calcium level and the type of bone lesion, some intestinal ability of net calcium transfer is preserved, though in a rather unpredictable fashion from one patient to another. The healing of florid osteomalacia was followed on serial bone biopsies and confirmed that the absorbed calcium can be utilized by the bone matrix in the absence of vitamin D. Recalcification started in the depth of osteoid seams and progressed eccentrically until remineralization of most of the trabeculae was achieved. Clinical results were satisfactory as bone pain and the occurrence of spontaneous fractures subsided. Yet this does not mean that the calcification pattern was a physiological one, since the bone density remained uneven and coarsely granular on microradiographs.

The comparison of the clinical course and of the biochemical pattern of the two groups deserves further comment. Serum phosphorus levels from the eighth month and thereafter were somewhat lower in group II, though not statistically different from group I. This was also true of the Ca × P products, but despite this apparent similarity metastatic calcifications were rare in calcium carbonate treated patients. This paradox is only superficial as we found that extra-skeletal deposits were only liable to occur in cases with severe resorption, where no unmineralized zones were left in the bone, capable of soaking up the Ca and P ions in excess [1]. In other terms, the risk of soft tissue deposits appeared to depend not only on the Ca × P products, but also on the presence of a remaining "calcium-arid compartment" in the skeleton.

The pattern of serum calcium and alkaline phosphatase curves is in keeping with the clinical and radiological evidence for the efficiency of a high calcium intake in preventing secondary hyperparathyroidism. The serum calcium levels were comparable in both groups throughout the long-term evolution. Conversely, the alkaline phosphatase remained remarkably stable in the calcium treated group, as opposed to a steady rise in the "dialysis alone" group. If one accepts the notion that this enzyme reflects the rate of PTH-stimulated osteoclastic resorption [15, 16, 19, 23], it appears that patients treated by dialysis alone maintained a constant serum calcium level at the expense of their skeleton.

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